



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PV/398/PCT	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/CZ 03/00056	International filing date (day/month/year) 21.10.2003	Priority date (day/month/year) 25.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/4406		
Applicant LECIVA, A.S.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.  
  
☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand  09.04.2004	Date of completion of this report  03.03.2005
Name and mailing address of the International preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Elliott, A  Telephone No. +49 89 2399-8218  

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EXAMINATION REPORT**

International application No. PCT/CZ 03/00056

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1, 2, 4-11 as originally filed  
3, 3a received on 19.01.2005 with letter of 13.01.2005

**Claims, Numbers**

8 (part), 9-16 as originally filed  
1-7, 8 (part) received on 19.01.2005 with letter of 13.01.2005

**Drawings, Sheets**

1/8-8/8 received on 30.10.2003 with letter of 30.10.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-16
	No: Claims	-
Inventive step (IS)	Yes: Claims	1-16
	No: Claims	-
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	-

2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CZ 03/00056

The application relates to crystalline, hydrated forms of risedronic acid wherein the sodium and water contents lie within particular limits with respect to each other.

The following documents have been taken into account:

- D1: WO 03/086355 A (TEVA PHARMACEUTICAL INDUSTRIES LTD) 23 October 2003 (2003-10-23)
- D2: US-A-2003195170
- D3: GOSSMAN W L ET AL: "Three hydrates of the bisphosphate risedronate, consisting of one molecular and two ionic structures" ACTA CRYSTALLOGRAPHICA SECTION C, vol. c59, 11 January 2003 (2003-01-11), pages m33-m36, XP009024776 ISSN: 0108-2701
- D4: WO 01/56983 A (PROCTER & GAMBLE) 9 August 2001 (2001-08-09)
- D5: KUSHIDA K: "Sodium risedronate hydrate" RINSHO TO YAKUBUTSU CHIRYO, vol. 21, no. 10, 2002, pages 1040-1, XP001157194 ISSN: 0913-7505
- D6: REDMAN-FUREY N L ET AL: "Thermoanalytical characterisation of the hydration states of risedronate" PROCEEDINGS OF THE NATAS ANNUAL CONFERENCE ON THERMAL ANALYSIS AND APPLICATIONS, no. 30th, 21 - 22 September 2002, pages 733-8, XP009024613

**Re Item VIII.**

A discrepancy was discovered in the way in which the weight percent of sodium and crystalline water was calculated. If, as originally filed, the calculations are done based in the anhydrous substance, the compounds of claims 2 and 3 as originally filed, if pure, would fall outside the ranges given for sodium and water content. If, on the other hand, these weight percentages were to be with respect to the weight of the whole molecule, the compound of claims 2 and 3 falls within the given ranges. Hence amendments to the claims and the corresponding part of the description are considered to be allowable as the correction of an obvious error.

**Re Item V.**

The prior art discloses a number of hydrated forms of sodium risedronate:

D4 - the hemipentahydrate and monohydrate of risedronate sodium.

D5 - again the hemipentahydrate of risedronate sodium.

D6 - again the hemipentahydrate and monohydrate of risedronate sodium

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The monohydrate and hemipentahydrate of risedronate sodium have the following sodium and water of crystallisation contents:

	%Na based on the anhydrous substance	%Na based on the whole molecule	%H <sub>2</sub> O
monohydrate	7.54%	7.1%	5.58%
hemipentahydrate	7.54%	6.57%	12.86%

The weight percentages are outside the ranges stated in modified claim 1. Claims 1-11 are therefore novel. Claims 12 to 15 directed to a method of preparing the novel hydrated forms of claims 1-11 are therefore also to be regarded as novel as is the pharmaceutical composition of claim 16.

As regards inventive step, the method of preparing the monohydrate and hemipentahydrate forms of risedronate sodium in D4 would appear very similar if not the same as that of claims 12-15. However, D4 also indicates that the product is a mixture of the hemipentahydrate and the monohydrate so that the skilled person has no incentive from D4 to use D4's method to prepare other hydrated forms of risedronate sodium. An inventive step is therefore acknowledged for all claims.

**Re Item VI.**

D1, published after the present application's filing date is not to be considered prior art under Rule 64.3 PCT. This document addresses polymorphs of risedronate sodium and only mentions the hemipentahydrate as a hydrated form.

D2, published in the present application's priority interval, is also not to be considered as prior art under Rule 64.3 PCT. D2's disclosure is the same as D1's.

D3, again published in the present application's priority interval, is also not to be considered as prior art under Rule 64.3 PCT. D3 discloses the dihydrate and hemipentahydrate of risedronate sodium.

**Re Item VII.**

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The dependency of claim 14 is incorrect.

The term risedronate stands for both risedronic acid and its pharmaceutically acceptable salts.

The term risedronate sodium salt monohydrate refers to a crystalline form of monosodium 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonate which contains from 5 to 7.1 w.% of water and from 5.5 to 7.5% of sodium, based on the whole molecule.

The term risedronate sodium salt pentahemihydrate stands for a crystalline form of monosodium 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonate which contains from 11.9 to 13.9 w.% of water and from 5.5 to 7.5% of sodium, based on the whole molecule.

The term risedronate sodium salt pentahydrate stands for a crystalline form of monosodium 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonate which contains from 20 to 23 w.% of water and from 5.5 to 7.5% of sodium, based on the whole molecule.

The term risedronate disodium salt monohydrate stands for a crystalline form of disodium 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonate which contains from 4.5 to 6.5 % of water and from 13 to 15% of sodium based on the anhydrous salt.

The term risedronate trisodium salt trihydrate stands for a crystalline form of trisodium 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonate which contains from 12 to 14 % of water and from 19 to 21% of sodium based on the anhydrous salt.

If not specified otherwise, all the percentage data herein are given in weight percents.

Our invention concerns sodium 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonate (sodium risedronate) in so-far-undocumented crystalline forms. More specifically, they are hydrates which contain 6.4 up to 22% of sodium and simultaneously 15 up to 23% of crystalline water if the sodium content is lower than 7.5%, based on the whole molecule, or 4.5 up to 18% if the sodium content is equal to or higher than 13 weight %, based on the anhydrous substance.

An useful example of such a hydrate is a modification that is characterized by water content 20 up to 23%, specially with 22.8 w.% of water, and sodium content 5.5 up to 7.5%, specially 6.4 up to 6.7 w.%. The specified water content is built in the crystal lattice and the mentioned crystalline modification is thermodynamically stable. By drying with several different drying regimes, the mentioned crystalline modification was dried to the water content corresponding to the pentahemihydrate, the monohydrate and the anhydrous form of sodium 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonate. When the substance is left

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standing on the air, the water content stabilizes spontaneously at the original level. Time that it takes for the water content to stabilize depends on relative humidity in the environment in

AMENDED SHEET

## CLAIMS

1. A crystalline, hydrated form of the sodium salt of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid, wherein the form contains from 6.4 up to 22 weight % of sodium and 15 up to 23 weight % of crystalline water if the sodium content is lower than 7.5 weight %, based on the whole molecule, or 4.5 up to 18 weight % of crystalline water if the sodium content is equal to or higher than 13 weight %, based on the anhydrous substance.
2. The crystalline form according to claim 1, which is pentahydrate of the monosodium salt of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid, wherein said form contains 20 up to 23 weight % of water built in the crystal lattice and 5.5 up to 7.5 % of sodium, based on the whole molecule.
3. The crystalline form according to claim 2 wherein said form contains 22.8 weight % of water built in the crystal lattice and 6.4 up to 6.7 % of sodium, based on the whole molecule.
4. The crystalline form according to claims 2 or 3 wherein said form shows a powder X-ray diffraction pattern with interplanar distances  $d$  approximately 16.3; 13.0; 9.1 and 4.9 Å.
5. The crystalline form according to claims 2 or 3 wherein said form shows the infrared spectrum with bands 1169; 1060; 1046 and 891  $\text{cm}^{-1}$ .
6. The crystalline form according to claims 2 or 3 thermogravimetric analysis of which shows a plateau at temperature of about 173 °C.
7. The crystalline form according to claims 2 or 3 the  $^{31}\text{P}$  CP-MAS NMR spectrum of which shows signals 13.7 and 20.0 ppm.
8. The crystalline form according to claim 1, which is trihydrate of the trisodium salt of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid, wherein said form contains